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| Set | Items | Description |
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| S1 | 505 | APAF AND APOPTOSIS |
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| S3 | 6 | AU='SHATTUCK DONNA' OR AU='SHATTUCK DONNA M' |
| S4 | 5 | AU='RUSSELL DEANNA L' |
| S5 | 5 | E3-E3 |
| S6 | 23 | AU='ABKEVICH V' OR AU='ABKEVICH V I' OR AU='ABKEVICH VICTOR' OR AU='ABKEVICH VICTOR I' |
| S7 | 13 | AU='NEFF CHRIS' OR AU='NEFF CHRIS D' OR AU='NEFF CHRISTOPHER' OR AU='NEFF CHRISTOPHER D' OR AU='NEFF CHRISTOPHER W' |
| S8 | 35 | S3 OR S4 OR S5 OR S6 OR S7 |
| S9 | 0 | S1 AND S8 |

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2/7/1
DIALOG(R)File 5:Biosis Previews(R)


0015098991 BIOSIS NO.: 200500004239
Reduced %%%Apaf%%%-1 expression in human cutaneous melanomas
AUTHOR: Dai D L; Martinka M; Bush J A; Li G (Reprint)
AUTHOR ADDRESS: Jack Bell Res Ctr, 2660 Oak St, Vancouver, BC, V6H 3Z6, Canada**Canada
AUTHOR E-MAIL ADDRESS: gangli@interchange.ubc.ca
JOURNAL: British Journal of Cancer 91 (6): p1089-1095 September 13, 2004 2004
MEDIUM: print
ISSN: 0007-0920 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Malignant melanoma is a life-threatening skin cancer due to its highly metastatic character and resistance to radio- and chemotherapy. It is believed that the ability to evade %%%apoptosis%%% is the key mechanism for the rapid growth of cancer cells. However, the exact mechanism for failure in the apoptotic pathway in melanoma cells is unclear. p53, the most frequently %%%mutated%%% tumour suppressor gene in human cancers, is a key %%%apoptosis%%% inducer. However, p53 %%%mutation%%% is only found in 15-20% of melanoma biopsies. Recently, it

was found that %%%Apaf%%%-1, a downstream target of p53, is inactivated in metastatic melanoma. Specifically, loss of heterozygosity (LOH) of the %%%Apaf%%%-1 gene was found in 40% of metastatic melanoma. To determine if loss of %%%Apaf%%%-1 expression is indeed involved in melanoma progression, we employed the tissue microarray technology and examined %%%Apaf%%%-1 expression in 70 human primary malignant melanoma biopsies by immunohistochemistry. Our data showed that %%%Apaf%%%-1 expression is significantly reduced in melanoma cells compared with normal nevi (chi2 = 6.02, P = 0.014). Our results also revealed that loss of %%%Apaf%%%-1 was not associated with the tumour thickness, ulceration or subtype, patient's gender, age and 5-year survival. In addition, our in vitro %%%apoptosis%%% assay revealed that overexpression of %%%Apaf%%%-1 can sensitise melanoma cells to anticancer drug treatment. Taken together, our data indicate that %%%Apaf%%%-1 expression is significantly reduced in human melanoma and that %%%Apaf%%%-1 may serve as a therapeutic target in melanoma.

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DIALOG(R)File 5:Biosis Previews(R)


0014992525 BIOSIS NO.: 200400363314
The Caenorhabditis elegans pvl-5 gene protects hypodermal cells from ced-3-dependent, ced-4-independent cell death
AUTHOR: Joshi Pradeep; Eisenmann David M (Reprint)
AUTHOR ADDRESS: Dept Biol Sci, Univ Maryland Baltimore Cty, 1000 Hilltop Circle, Baltimore, MD, 21250, USA**USA
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JOURNAL: Genetics 167 (2): p673-685 June 2004 2004
MEDIUM: print
ISSN: 0016-6731 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Programmed cell death (PCD) is regulated by multiple evolutionarily conserved mechanisms to ensure by the survival of the cell. Here we describe pvl-5, a gene that likely regulates PCD in Caenorhabditis elegans. In wild-type hermaphrodites at the L2 stage there are 11 Pn.p hypodermal cells in the ventral midline arrayed along the anterior-posterior axis and 6 of these cells become the vulval precursor cells. In pvl-5(ga87) animals there are fewer Pn.p cells (average of 7.0) present at this time. Lineage analysis reveals that the missing Pn.p cells die around the time of the L1 molt in a manner that often resembles the programmed cell deaths that occur normally in C. elegans development.

This Pn.p cell death is suppressed by %%%mutations%%% in the caspase gene ced-3 and in the bc1-2 homolog ced-9, Suggesting that the Pn.p cells are dying by PCD in pvl-5 mutants. Surprisingly, the Pn.p cell death is not suppressed by loss of ced-4 function. ced-4 (%%%Apaf%%%-1) is required for all previously known apoptotic cell deaths in C. elegans. This suggests that loss of pvl 5 function leads to the activation of a ced-3-dependent, ced-4-independent form of PCD and that pvl-5 may, normally function to protect Cells from inappropriate activation of the apoptotic pathway.

2/7/3
DIALOG(R)File 5:Biosis Previews(R)


0014911875 BIOSIS NO.: 200400282632
Mitochondrial translocation of p53 and mitochondrial membrane potential ( DELTAPSIm) dissipation are early events in staurosporine-induced %%%apoptosis%%% of wild type and %%%mutated%%% p53 epithelial cells
AUTHOR: Charlot J F; Pretet J L; Haughey C; Mougin C (Reprint)
AUTHOR ADDRESS: Biol Cellulaire & Mol LabEA 3181, CHU Jean Minjoz, 2 Blvd Fleming, F-25030, Besancon, France**France
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JOURNAL: Apoptosis 9 (3): p333-343 May 2004 2004
MEDIUM: print
ISSN: 1360-8185 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mitochondrial localization of p53 is an important event in p53-dependent %%%apoptosis%%%. Some p53 mutants defective for transcription also facilitate %%%apoptosis%%% through changes of the mitochondria. Here, %%%apoptosis%%% of HeLa and CaSki cells (p53wt), C33A and HaCat cells (p53mt) and SaOs-2 cells (p53 deficient) was induced by 300 nM staurosporine. We showed that wild-type p53, as well as p53 mutants, were transiently located to the mitochondria with changes in the mitochondrial membrane potential (DELTAPSIm). However, in C33A cells harboring a p53 %%%mutated%%% on its DNA binding domain, DELTAPSIm collapse and Sub-G1 DNA content were reduced compared to p53wt cells, whereas no significant difference was observed in HaCat cells with a p53 %%%mutated%%% on UV hot spots. In addition, inhibition of the mitochondrial permeability transition pores by cyclosporine A significantly reduced the DELTAPSIm loss and the sub-G1 DNA content in p53 positive cells. These results indicate that DELTAPSIm collapse is an early and necessary event, which plays an important role in

%%%apoptosis%%% of immortal mammalian cells.

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DIALOG(R)File 5:Biosis Previews(R)


0014894389 BIOSIS NO.: 200400265146
%%%Apoptosis%%% defects and chemotherapy resistance: molecular interaction maps and networks
AUTHOR: Pommier Yves (Reprint); Sordet Olivier; Antony Smitha; Hayward Richard L; Kohn Kurt W
AUTHOR ADDRESS: Lab Genom Stabil, Inst Pasteur, Pavillon Fernbach,Room 26,25 Rue Dr Roux, F-75724, Paris, France**France
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JOURNAL: Oncogene 23 (16): p2934-2949 April 12, 2004 2004
MEDIUM: print
ISSN: 0950-9232 _(ISSN print)
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Intrinsic (innate) and acquired (adaptive) resistance to chemotherapy critically limits the outcome of cancer treatments. For many years, it was assumed that the interaction of a drug with its molecular target would yield a lethal lesion, and that determinants of intrinsic drug resistance should therefore be sought either at the target level (quantitative changes or/and %%%mutations%%%) or upstream of this interaction, in drug metabolism or drug transport mechanisms. It is now apparent that independent of the factors above, cellular responses to a molecular lesion can determine the outcome of therapy. This review will focus on programmed cell death (%%%apoptosis%%%) and on survival pathways (Bcl-2, %%%Apaf%%%-1, AKT, NF-kappaB) involved in multidrug resistance. We will present our molecular interaction mapping conventions to summarize the AKT and IkappaB/NF-kappaB networks. They complement the p53, Chk2 and c-Abl maps published recently. We will also introduce the 'permissive %%%apoptosis%%%-resistance' model for the selection of multidrug-resistant cells.

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DIALOG(R)File 5:Biosis Previews(R)


0014827163 BIOSIS NO.: 200400194796
Enhanced ES - derived neurosphere formation with increased cell viability

supports a model of default differentiation of ES cells into primitive neural stem cells.

AUTHOR: Smukler S R (Reprint); Xu S (Reprint); van der Kooy D (Reprint)
AUTHOR ADDRESS: Univ. of Toronto, ON, ON, Canada**Canada

JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 124.6 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mechanisms governing the emergence of the earliest neural precursors during development remain incompletely characterized. We have demonstrated that most ES cells will acquire a neural identity by a default mechanism when cultured in serum-and growth factor-free conditions. A very small percentage (apprx0.2%) exhibit characteristics of primitive neural stem cells (NSCs) in LIF, proliferating to form neurospheres (NSs). The question remains as to whether the default differentiation pathway specifically gives rise to NSCs or simply to cells of the neural lineage. ES cells undergo a survival challenge in serum-free conditions, resulting in extensive cell death, limiting the number of NSCs that can survive to proliferate. Addition of the survival factor N-acetyl-L-cysteine (NAC) increased cell viability and NS formation. The cAMP/PKA pathway was explored as a physiological modulator of cell survival. cAMP analogue application or adenylate cyclase (AC) activation increased cell viability and NS formation. Inhibition of AC or PKA reduced basal and cAMP-stimulated NS formation. NAC and cAMP synergized to enhance NS formation (up to 100-fold), such that apprx20% of ES cells formed NSs. NAC and cAMP were effective even when added after the majority of ES cells already expressed nestin, suggesting that they were not effecting the NS increase through an instructive role in early fate determination. %%%APAF%%%-/-, Caspase9-/-, and AIF-/-ES cells, which have a survival advantage conferred by %%%mutations%%% in apoptotic signalling pathways, displayed enhanced NS formation. Further, the NAC and cAMP effects were largely attenuated in these cells. We conclude that the default differentiation of ES cells is indeed directly into a primitive NSC, and that increasing cell viability with exogenous survival factors, activation of the cAMP/PKA pathway, or by genetic interference with %%%apoptosis%%% facilitates the survival and proliferation of these cells.

DIALOG(R)File 5:Biosis Previews(R)


0014805535 BIOSIS NO.: 200400176292
The organellular chloride channel protein CLIC4/mtCLIC translocates to the nucleus in response to cellular stress and accelerates %%%apoptosis%%%.
AUTHOR: Suh Kwang S; Mutoh Michihiro; Nagashima Kunio; Fernandez-Salas Ester; Edwards Lindsay E; Hayes Daniel D; Crutchley John M; Marin Keith G ; Dumont Rebecca A; Levy Joshua M; Cheng Christina; Garfield Susan; Yuspa Stuart H (Reprint)
AUTHOR ADDRESS: Laboratory of Cellular Carcinogenesis and Tumor Promotion, Center for Cancer Research, NCI, National Institutes of Health (NIH), Bethesda, MD, 20892, USA**USA
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JOURNAL: Journal of Biological Chemistry 279 (6): p4632-4641 February 6, 2004 2004
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CLIC4/mtCLIC, a chloride intracellular channel protein, localizes to the mitochondria and cytoplasm of keratinocytes and participates in the apoptotic response to stress. We now show that multiple stress inducers cause the translocation of cytoplasmic CLIC4 to the nucleus. Immunogold electron microscopy and confocal analyses indicate that nuclear CLIC4 is detected prior to the apoptotic phenotype. CLIC4 associates with the Ran, NTF2, and Importin-alpha nuclear import complexes in immunoprecipitates of lysates from cells treated with apoptotic/stress-inducing agents. Deletion or %%%mutation%%% of the nuclear localization signal in the C terminus of CLIC4 eliminates nuclear translocation, whereas N terminus deletion enhances nuclear localization. Targeting CLIC4 to the nucleus via adenoviral transduction accelerates %%%apoptosis%%% when compared with cytoplasmic CLIC4, and only nuclear-targeted CLIC4 causes %%%apoptosis%%% in %%%Apaf%%% null mouse fibroblasts or in Bcl-2-overexpressing keratinocytes. These results indicate that CLIC4 nuclear translocation is an integral part of the cellular response to stress and may contribute to the initiation of nuclear alterations that are associated with %%%apoptosis%%%.

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0014804966 BIOSIS NO.: 200400175723
Cytochrome c and dATP-dependent formation of %%%Apaf%%%-1/caspase-9 complex initiates an apoptotic protease cascade.
AUTHOR: Li Peng; Nijhawan Deepak; Budihardjo Imawati; Srinivasula Srinivasa M; Ahmad Manzoor; Alnemri Emad S; Wang Xiaodong (Reprint)
AUTHOR ADDRESS: Howard Hughes Medical Institute and Department of Biochemistry, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75235, USA**USA
JOURNAL: Cell S116 (2): p479-489 January 23, 2004 2004
MEDIUM: print
ISSN: 0092-8674
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We report here the purification of the third protein factor, %%%Apaf%%%-3, that participates in caspase-3 activation in vitro. %%%Apaf%%%-3 was identified as a member of the caspase family, caspase-9. Caspase-9 and %%%Apaf%%%-1 bind to each other via their respective NH2-terminal CED-3 homologous domains in the presence of cytochrome c and dATP, an event that leads to caspase-9 activation. Activated caspase-9 in turn cleaves and activates caspase-3. Depletion of caspase-9 from S-100 extracts diminished caspase-3 activation. %%%Mutation%%% of the active site of caspase-9 attenuated the activation of caspase-3 and cellular apoptotic response in vivo, indicating that caspase-9 is the most upstream member of the apoptotic protease cascade that is triggered by cytochrome c and dATP.

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DIALOG(R)File 5:Biosis Previews(R)


0014802638 BIOSIS NO.: 200400173395
Functional evaluation of the apoptosome in renal cell carcinoma.
AUTHOR: Gerhard M C; Zantl N; Weirich G; Schlieep S; Seiffert B; Haecker G (Reprint)
AUTHOR ADDRESS: Institute for Medical Microbiology, Immunology and Hygiene, Trogerstrasse 9, Munich, D-81675, Germany**Germany
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JOURNAL: British Journal of Cancer 89 (11): p2147-2154 1 December, 2003 2003
MEDIUM: print
ISSN: 0007-0920 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Renal cell carcinoma (RCC) responds very poorly to chemo- or radiotherapy. Renal cell carcinoma cell lines have been described to be resistant to %%%apoptosis%%%-inducing stimuli and to lack caspase expression. Here, we provide a structural and functional assessment of the apoptosome, the central caspase-activating signalling complex and a candidate for %%%apoptosis%%%-inactivating %%%mutations%%%. Cells from RCC cell lines and clinical samples isolated from RCC patients were included. Apoptosome function was measured as quantitative activation of caspases in protein extracts. In all five cell lines and in 19 out of 20 primary clear cell RCC samples, the expression of apoptosome components and caspase activation appeared normal. Of the four nonclear cell RCC that could be included, both oncocytomas gave no response to cytochrome c (in one case, no %%%Apaf%%%-1 was detected), one chromophobe RCC lacked caspase-9 and failed to activate caspase-3 in response to cytochrome c, and one papillary RCC showed good caspase activation despite the lack of caspase-7. Experiments utilising a peptide derived from Smac/DIABLO gave no indication that inhibitor of %%%apoptosis%%% proteins might exert an inhibiting effect in primary clear cell RCC. Thus, the apoptosome signalling complex is intact in human (clear cell) RCC, and an %%%apoptosis%%% defect must be located at other, probably upstream, sites.

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0014780217 BIOSIS NO.: 200400146878

Comprehensive profiling of %%%apoptosis%%% regulators in B-CLL reveals overexpression of Bmf and Noxa and links cytostatic drug-induced Puma upregulation with IGVH status.

AUTHOR: Kater Arnon P (Reprint); Mackus Wendelina J M (Reprint); Grummels A ; van Lier Rene A W; van Oers Marinus H J (Reprint); Eldering Eric (Reprint)
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JOURNAL: Blood 102 (11): p428a-429a November 16, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: At present, an integrated understanding of dysregulated %%%apoptosis%%% in B cell chronic lymphocytic leukemia (B-CLL) is lacking. In order to comprehensively quantify expression of virtually all direct regulators of %%%apoptosis%%%, we applied a novel multiplex assay, reverse transcriptase-Multiplex Ligation-dependent Probe Amplification. This RT-MLPA assay targets 34 genes, and includes the Bcl-2 and IAP families and miscellaneous regulators such as Flip, PI-9, AIF and %%%Apaf%%%. Using this technique the %%%apoptosis%%% gene expression profile of B-CLL cells of 18 patients (8 patients with unmutated and 10 patients with %%%mutated%%% IgVH genes) was investigated in relation to (1) normal tonsilar B cell subsets, (2) IgVH %%%mutation%%% status, and (3) incubation with cytostatic drugs. In accord with the non-cycling, anti-apoptotic status of B-CLL cells in vivo, they displayed high constitutive expression of Bcl-2 and Flip, while Survivin, Bid and Bik were absent. Paradoxically, next to these protective changes B-CLL cells showed increased expression of apoptogenic BH3-only members Bmf and Noxa, which was confirmed on the protein level. Upon treatment of cells with either fludarabine, etoposide or chlorambucil in vitro, only the p53-responsive Puma was prominently induced. Moreover, the degree of Puma induction was more profound in cells of %%%mutated%%% IgVH B-CLL (15+8-fold in unmutated and 41+24-fold in %%%mutated%%% IgVH cases; P=0.0062). Thus, disturbed %%%apoptosis%%% in B-CLL is the net result of both protective and sensitising aberrations, and this delicate balance may be tipped via a p53-response. Our results suggest that the clinical distinction between B-CLL subgroups may be linked to differences in the p53-responsive, Puma-mediated %%%apoptosis%%% pathway.

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DIALOG(R)File 5:Biosis Previews(R)


0014778039 BIOSIS NO.: 200400144700
Tumor necrosis factor death receptor signaling cascade is required for amyloid-beta protein-induced neuron death.
AUTHOR: Li Rena; Yang Libang; Lindholm Kristina; Konishi Yoshihiro; Yue Xu; Hampel Harald; Zhang Dai; Shen Yong (Reprint)
AUTHOR ADDRESS: Haldeman Laboratory of Molecular and Cellular Neurobiology, Sun Health Research Institute, 10515 West Santa Fe Drive, Sun City, AZ, 85351, USA**USA
AUTHOR E-MAIL ADDRESS: rena.li@sunhealth.org; yong.shen@sunhealth.org
JOURNAL: Journal of Neuroscience 24 (7): p1760-1771 February 18, 2004 2004
MEDIUM: print
ISSN: 0270-6474 _(ISSN print)

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Tumor necrosis factor type I receptor (TNFRI), a death receptor, mediates %%%apoptosis%%% and plays a crucial role in the interaction between the nervous and immune systems. A direct link between death receptor activation and signal cascade-mediated neuron death in brains with neurodegenerative disorders remains inconclusive. Here, we show that amyloid-beta protein (Abeta), a major component of plaques in the Alzheimer's diseased brain, induces neuronal %%%apoptosis%%% through TNFRI by using primary neurons overexpressing TNFRI by viral infection or neurons from TNFRI knock-out mice. This was mediated via alteration of apoptotic protease-activating factor (%%%Apaf%%%-1) expression that in turn induced activation of nuclear factor kappaB (NF-kappaB). Abeta-induced neuronal %%%apoptosis%%% was reduced with lower %%%Apaf%%% -1 expression, and little NF-kappaB activation was found in the neurons with %%%mutated%%% %%%Apaf%%%-1 or a deletion of TNFRI compared with the cells from wild-type (WT) mice. Our studies suggest a novel neuronal response of Abeta, which occurs through a TNF receptor signaling cascade and a caspase-dependent death pathway.

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DIALOG(R)File 5:Biosis Previews(R)


0014766776 BIOSIS NO.: 200400134130
Frequent LOH at chromosome 12q22-23 and %%%Apaf%%%-1 inactivation in Glioblastoma.
AUTHOR: Watanabe Takuya; Hirota Yuichi; Arakawa Yasuaki; Fujisawa Hironori; Tachibana Osamu; Hasegawa Mitsuhiro; Yamashita Junkoh; Hayashi Yutaka (Reprint)
AUTHOR ADDRESS: Department of Neurosurgery, Graduate School of Medical Science, Kanazawa University, 13-1 Takaramachi, Kanazawa, Ishikawa, 920-8641, Japan**Japan
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JOURNAL: Brain Pathology 13 (4): p431-439 October 2003 2003
MEDIUM: print
ISSN: 1015-6305 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Glioblastoma (GB) often has loss of heterozygosity on the chromosomes, 1p, 10p, 10q, 11p, 17p, 19q, 22q, and several others. In the

case of chromosome 12q, however, it remains to be seen whether LOH occurs. %%%Apaf%%%-1, the apoptotic protease activating factor-1, located at chromosome 12q22-23, is a major effecter of the p53 mediated %%%apoptosis%%% pathway, and %%%Apaf%%%-1 inactivation due to chromosome 12q22-23 LOH and hypermethylation may be involved in some of the neoplasms in malignancy. However, little is known about the frequency of the 12q22-23 LOH or the state of %%%Apaf%%%-1 in GB. To elucidate their involvement in GB, we analyzed a series of 33 GBs for chromosome 12q22-23 LOH, %%%Apaf%%%-1 mRNA expression, and %%%Apaf%%%-1 protein expression, using microsatellite analysis, reverse transcription (RT)-PCR analysis, and immunohistochemical (IHC) analysis, respectively. We also evaluated if and how the 12q22-23 LOH correlated with the p53 gene %%%mutation%%% and EGFR gene amplification. Chromosome 12q22-23LOH was detected in 14 (42%) of 33 cases. Among the examined cases with LOH at 12q22-23, a low expression of %%%Apaf%%%-1 mRNA was detected in 9 (69%) of 13 cases, and a low expression of %%%Apaf%%%-1 protein was detected in 12 (86%) of 14 cases. The 12q22-23 LOH was significantly correlated with low expression of mRNA and protein ($p<0.05$, $p<0.001$ respectively). The p53 gene %%%mutation%%% and EGFR gene amplification were found in 13 cases (39%) and 8 cases (24%), respectively, and these gene alterations were inversely correlated. However, 12q22-23 LOH had no correlations with the p53 gene %%%mutation%%% or EGFR gene amplification. Six of 9 GBs (67%) with neither p53 gene %%%mutation%%% nor EGFR gene amplification tested positive for 12q22-23 LOH. These GBs are likely to belong to another subset independent from the 2 common genetic subsets in GB (one with p53 gene %%%mutation%%% and without EGFR gene amplification, and the other with EGFR gene amplification and without p53 gene %%%mutation%%%). Twenty-three (70%) out of the 33 GBs with the 12q22-23 LOH also tested positive for %%%Apaf%%%-1 inactivation or p53 gene %%%mutation%%%. This high frequency of alterations in the %%%apoptosis%%%-associated factors prompts a speculation that abrogation of the %%%Apaf%%%-1 and p53 mediated %%%apoptosis%%% pathway may play an important role in the tumorigenesis of GB.



0014762890 BIOSIS NO.: 200400143647
Molecular mechanisms for apigenin-induced cell-cycle arrest and %%%apoptosis%%% of hormone refractory human prostate carcinoma DU145 cells.
AUTHOR: Shukla Sanjeev; Gupta Sanjay (Reprint)
AUTHOR ADDRESS: Department of Urology, James and Eilleen Dicke Research Laboratory, Case Western Reserve University, 10900 Euclid Avenue,

Cleveland, OH, 44106, USA**USA
JOURNAL: Molecular Carcinogenesis 39 (2): p114-126 February 2004 2004
MEDIUM: print
ISSN: 0899-1987
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Development of effective agents for treatment of hormone-refractory prostate cancer has become a national medical priority. We have reported recently that apigenin (4',5,7-trihydroxyflavone), found in many common fruits and vegetables, has shown remarkable effects in inhibiting cell growth and inducing %%%apoptosis%%% in many human prostate carcinoma cells. Here we demonstrate the molecular mechanism of inhibitory action of apigenin on androgen-refractory human prostate carcinoma DU145 cells that have %%%mutations%%% in the tumor suppressor gene p53 and pRb. Treatment of cells with apigenin resulted in a dose- and time-dependent inhibition of growth, colony formation, and G1 phase arrest of the cell cycle. This effect was associated with a marked decrease in the protein expression of cyclin D1, D2, and E and their activating partner, cyclin-dependent kinase (cdk)2, 4, and 6, with concomitant upregulation of WAF1/p21, KIP1/p27, INK4a/p16, and INK4c/p18. The induction of WAF1/p21 and its growth inhibitory effects by apigenin appears to be independent of p53 and pRb status of these cells. Apigenin treatment also resulted in alteration in Bax/Bcl2 ratio in favor of %%%apoptosis%%%, which was associated with the release of cytochrome c and induction of apoptotic protease-activating factor-1 (%%%Apaf%%%-1). This effect was found to result in a significant increase in cleaved fragments of caspase-9, -3, and poly(ADP-ribose) polymerase (PARP). Further, apigenin treatment resulted in downmodulation of the constitutive expression of nuclear factor-kappaB (NF-kappaB)/p65 and NF-kappaB/p50 in the nuclear fraction that correlated with an increase in the expression of IkappaB-alpha (IkappaBalpha) in the cytosol. Taken together, we concluded that molecular mechanisms during apigenin-mediated growth inhibition and induction of %%%apoptosis%%% in DU145 cells was due to (1) modulation in cell-cycle machinery, (2) disruption of mitochondrial function, and (3) NF-kappaB inhibition.

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DIALOG(R)File 5:Biosis Previews(R)


0014608402 BIOSIS NO.: 200300567121
NMR structure of the %%%apoptosis%%%- and inflammation-related NALP1 pyrin

domain.
AUTHOR: Hiller Sebastian; Kohl Andreas; Fiorito Francesco; Herrmann Torsten ; Wider Gerhard; Tschopp Jurg; Grutter Markus G (Reprint); Wuthrich Kurt
AUTHOR ADDRESS: Biochemisches Institut, Universitat Zurich, CH-8057, Zurich, Switzerland**Switzerland
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JOURNAL: Structure (Cambridge) 11 (10): p1199-1205 October 2003 2003
MEDIUM: print
ISSN: 0969-2126 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Signaling in %%%apoptosis%%% and inflammation is often mediated by proteins of the death domain superfamily in the Fas/FADD/Caspase-8 or the %%%Apaf%%%-1/Caspase-9 pathways. This superfamily currently comprises the death domain (DD), death effector domain (DED), caspase recruitment domain (CARD), and pyrin domain (PYD) subfamilies. The PYD subfamily is most abundant, but three-dimensional structures are only available for the subfamilies DD, DED, and CARD, which have an antiparallel arrangement of six alpha helices as common fold. This paper presents the NMR structure of PYD of NALP1, a protein that is involved in the innate immune response and is a component of the inflammasome. The structure of NALP1 PYD differs from all other known death domain superfamily structures in that the third alpha helix is replaced by a flexibly disordered loop. This unique feature appears to relate to the molecular basis of familial Mediterranean fever (FMF), a genetic disease caused by single-point %%%mutations%%%.

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DIALOG(R)File 5:Biosis Previews(R)


0014318601 BIOSIS NO.: 200300273134
Signaling of cell death and cell survival following focal cerebral ischemia: Life and death struggle in the penumbra.
AUTHOR: Ferrer Isidro (Reprint); Planas Anna Maria
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JOURNAL: Journal of Neuropathology and Experimental Neurology 62 (4): p 329-339 April 2003 2003
MEDIUM: print

ISSN: 0022-3069 _(ISSN print)
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Focal ischemia by middle cerebral artery occlusion (MCAO) results in necrosis at the infarct core and activation of complex signal pathways for cell death and cell survival in the penumbra. Recent studies have shown activation of the extrinsic and intrinsic pathways of caspase-mediated cell death, as well as activation of the caspase-independent signaling pathway of %%%apoptosis%%% in several paradigms of focal cerebral ischemia by transient MCAO to adult rats and mice. The extrinsic pathway (cell-death receptor pathway) is initiated by activation of the Fas receptor after binding to the Fas ligand (Fas-L); increased Fas and Fas-L expression has been shown following focal ischemia. Moreover, focal ischemia is greatly reduced in mice expressing %%%mutated%%% (nonfunctional) Fas. Increased expression of caspase-1, -3, -8, and -9, and of cleaved caspase-8, has been observed in the penumbra. Activation of the intrinsic (mitochondrial) pathway following focal ischemia is triggered by Bax translocation to and competition with Bcl-2 and other members of the Bcl-2 family in the mitochondria membrane that is followed by cytochrome c release to the cytosol. Bcl-2 over-expression reduces infarct size. Cytochrome c binds to %%%Apaf%%%-1 and dATP and recruits and cleaves pro-caspase-9 in the apoptosome. Both caspase-8 and caspase-9 activate caspase-3, among other caspases, which in turn cleave several crucial substrates, including the DNA-repairing enzyme poly(ADP-ribose) polymerase (PARP), into fragments of 89 and 28 kDa. Inhibition of caspase-3 reduces the infarct size, further supporting caspase-3 activation following transient MCAO. In addition, caspase-8 cleaves Bid, the truncated form of which has the capacity to translocate to the mitochondria and induce cytochrome c release. The volume of brain infarct is greatly reduced in Bid-deficient mice, thus indicating activation of the mitochondrial pathway by cell-death receptors following focal ischemia. Recent studies have shown the mitochondrial release of other factors; Smac/DIABLO (Smac: second mitochondrial activator of caspases; DIABLO: direct IAP binding protein with low pI) binds to and neutralizes the effects of the X-linked inhibitor of %%%apoptosis%%% (XIAP). Finally, %%%apoptosis%%%-inducing factor (AIF) translocates to the mitochondria and the nucleus following focal ischemia and produces peripheral chromatin condensation and large-scale DNA strands, thus leading to the caspase-independent cell death pathway of %%%apoptosis%%%. Delineation of the pro-apoptotic and pro-survival signals in the penumbra may not only increase understanding of the process but also help to rationalize strategies geared to reducing brain damage targeted at the periphery of the infarct core.

2/7/15
DIALOG(R)File 5:Biosis Previews(R)


0014071821 BIOSIS NO.: 200300030540
[Alteration of cell death-related genes in human diseases.]
ORIGINAL LANGUAGE TITLE: Implications physiopathologiques des alterations des genes impliques dans la regulation de la mort cellulaire.
AUTHOR: Solary Eric (Reprint); Bettaieb Ali; Dubrez-Daloz Laurence; Garrido Carmen
AUTHOR ADDRESS: Inserm U.517, IFR 100, EPHE, UFR de Medecine/Pharmacie, 7, boulevard Jeanne d'Arc, 21000, Dijon, France**France
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JOURNAL: M-S (Medecine Sciences) 18 (8-9): p861-873 Aout-Septembre 2002 2002
MEDIUM: print
ISSN: 0767-0974
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: French

ABSTRACT: Cell death by %%%apoptosis%%% is a fundamental process that regulates tissue development and homeostasis. Deregulation of this process is involved in a number of human diseases and this deregulation can be related to inherited or acquired genetic abnormalities of proteins involved in the death machinery. Most inherited %%%mutations%%% interfere with the death receptor signalling pathways, including Fas, Fas-ligand or caspase-10 %%%mutations%%% in the Canale-Smith syndrome, deletion of NEMO (IKKgamma) gene in familial incontinentia pigmenti and %%%mutations%%% in the extracellular domains of the 55 kDa TNF receptor in a dominant autoinflammatory syndrome. Familial Mediterranean fever was related to %%%mutations%%% in the MEFV gene whose product interacts with the pro-apoptotic protein ASC. Perforin gene defects were identified in familial hemophagocytic lymphohistiocytosis whereas alterations of naip gene, that encodes a caspase inhibitory protein, increase the severity of spinal amyotrophy. In human tumors, three mechanisms were observed to account for acquired cell death gene alteration: chromosomal translocation leading to overexpression of a normal (Bcl-2) or %%%mutated%%% (Bcl-10, c-IAP2) protein, gene %%%mutation%%% leading to functional alterations of the protein (p53, Fas, Bax) and gene promoter hypermethylation that prevents the protein expression (caspase 8, %%%Apaf%%%-1, DAP kinase, TMS1). Depending on the disease, these genetic abnormalities can now be used as diagnostic tools, prognostic markers and therapeutic targets.

2/7/16
DIALOG(R)File 5:Biosis Previews(R)


0013875822 BIOSIS NO.: 200200469333
Strain-dependent neurodevelopmental abnormalities in caspase-3-deficient mice
AUTHOR: Leonard Jeffrey R; Klocke Barbara J; D'Sa Cleta; Flavell Richard A; Roth Kevin A (Reprint)
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JOURNAL: Journal of Neuropathology and Experimental Neurology 61 (8): p 673-677 August, 2002 2002
MEDIUM: print
ISSN: 0022-3069
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Targeted gene disruptions have revealed significant roles for caspase family members in the regulation of neuronal programmed cell death. Both caspase-3- and caspase-9-deficient mice exhibit a variably severe neurodevelopmental phenotype that may include marked ventricular zone expansion, exencephaly, and ectopic neuronal structures. Our previous studies of caspase-3- and caspase-9-deficient mice were performed using mice on mixed genetic backgrounds, raising the possibility that strain-specific genetic factors influence the effects of caspase deficiency on nervous system development. To directly test this hypothesis, we backcrossed the caspase-3 %%%mutation%%% for 7-10 generations onto pure C57BL/6J and 129X1/SvJ genetic backgrounds. Caspase-3-deficient 129X1/SvJ mice were uniformly and severely affected. These mice died during the perinatal period and exhibited marked neural precursor cell expansion and exencephaly. In contrast, caspase-3-deficient C57BL/6J mice reached adulthood, were fertile and showed minimal brain pathology. Intercrosses of C57BL/6J and 129X1/SvJ mutants revealed that the vast majority of caspase-3-/- F1 mice displayed the severe 129X1/SvJ-"like" phenotype. These findings are consistent with an incompletely penetrant strain-dependent genetic modifier (or modifiers) that alters the neurodevelopmental consequences of caspase-3 deficiency. Since caspase-9- and %%%Apaf%%%-1-deficient mice also display variably severe developmental neuropathology, this strain-dependent modifier(s) may be involved in the activation of a caspase-independent death pathway; alternatively, strain-dependent compensatory caspase activation and/or its inhibition may influence the severity of the

caspase-3-deficient neuronal phenotype.

2/7/17
DIALOG(R)File 5:Biosis Previews(R)


0013813471 BIOSIS NO.: 200200406982
CARD15 genetic variation in a Quebec population: Prevalence, genotype-phenotype relationship, and haplotype structure
AUTHOR: Vermeire Severine; Wild Gary; Kocher Kerry; Cousineau Josee; Dufresne Line; Bitton Alain; Langelier Diane; Pare Pierre; Lapointe Gilles; Cohen Albert; Daly Mark J; Rioux John D (Reprint)
AUTHOR ADDRESS: Human Medical and Population Genetics, Center for Genome Research, Whitehead Institute/MIT, One Kendall Square, Building 300, Cambridge, MA, 02139-1561, USA**USA
JOURNAL: American Journal of Human Genetics 71 (1): p74-83 July, 2002 2002
MEDIUM: print
ISSN: 0002-9297
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The caspase recruitment domain gene (CARD15) was recently identified as the underlying gene associated with the IBD1 locus that confers susceptibility to Crohn disease (CD). CARD15 is related to the NOD1/%%%Apaf%%%-1 family of %%%apoptosis%%% regulators, and three sequence variants (Arg702Trp, Gly908Arg, and Leu1007fsinsC) in the gene were demonstrated to be associated with CD. We collected a cohort of 231 patients with CD and 71 healthy control individuals from the Canadian province of Quebec, to determine the prevalence of these sequence variants in an independent population. Clinical records of all patients were systematically reviewed, and detailed phenotypic information was obtained. All patient DNA samples were genotyped for the three variants, thus enabling an analysis of genotype-phenotype correlations. In this cohort, 45.0% of patients with CD carried at least one variant in the CARD15 gene, compared with 9.0% of control individuals (P<10-7). Allele frequencies of Arg702Trp, Gly908Arg, and Leu1007fsinsC were 12.9%, 5.2%, and 10.3% in patients with CD, compared with 4.2%, 0.7%, and 0.7% in control individuals, respectively. Importantly, CARD15 mutants were seen with equal frequency in patients with familial and sporadic CD. Analysis of the relationship between genotype and phenotype convincingly demonstrates that CARD15 variants are significantly associated with ileal disease involvement, as opposed to strictly colonic disease (P<.001). Moreover, we were able to determine the haplotype structure surrounding this disease gene by genotyping 45 single-nucleotide polymorphisms (SNPs)

in a 177-kb region that contained the CARD15 gene. This structure helps clarify the history of these causal %%%mutations%%%. Finally, this analysis shows that CARD15 involvment with CD is detectable by use of publicly available SNPs alone.

2/7/18
DIALOG(R)File 5:Biosis Previews(R)


0013734885 BIOSIS NO.: 200200328396
Unrestrained caspase-dependent cell death caused by loss of Diap1 function requires the Drosophila %%%Apaf%%%-1 homolog, dark
AUTHOR: Rodriguez Antony; Chen Po; Oliver Holt; Abrams John M (Reprint)
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JOURNAL: EMBO (European Molecular Biology Organization) Journal 21 (9): p 2189-2197 May 1, 2002 2002
MEDIUM: print
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In mammals and Drosophila, apoptotic caspases are under positive control via the CED-4/%%%Apaf%%%-1/Dark adaptors and negative control via IAPs (inhibitor of %%%apoptosis%%% proteins). However, the in vivo genetic relationship between these opposing regulators is not known. In this study, we demonstrate that a dark %%%mutation%%% reverses catastrophic defects seen in Diap1 mutants and rescues cells specified for Diap1-regulated cell death in development and in response to genotoxic stress. We also find that dark function is required for hyperactivation of caspases which occurs in the absence of Diap1. Since the action of dark is epistatic to that of Diap1, these findings demonstrate that caspase-dependent cell death requires concurrent positive input through %%%Apaf%%%-1-like proteins together with disruption of IAP-caspase complexes.

2/7/19
DIALOG(R)File 5:Biosis Previews(R)


0013670205 BIOSIS NO.: 200200263716
The apoptosome is a target of Jun kinase in nitric oxide-induced cardiac

myocyte %%%apoptosis%%%
AUTHOR: Andreka Peter (Reprint); Dougherty Christopher (Reprint); Slepak Tatiana I (Reprint); Webster Keith A (Reprint); Bishopric Nanette H (Reprint)
AUTHOR ADDRESS: Univ of Miami Sch of Med, Miami, FL, USA**USA
JOURNAL: Circulation 104 (17 Supplement): pII.142 October 23, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001; 20011111
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ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/20
DIALOG(R)File 5:Biosis Previews(R)


0013644683 BIOSIS NO.: 200200238194
Co-transduction of %%%Apaf%%%-1 and caspase-9 highly enhances p53-mediated %%%apoptosis%%% in gliomas
AUTHOR: Shinoura N (Reprint); Sakurai S; Shibasaki F; Asai A; Kirino T; Hamada H
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JOURNAL: British Journal of Cancer 86 (4): p587-595 12 February, 2002 2002
MEDIUM: print
ISSN: 0007-0920
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Mutation%%% of the p53 gene plays a critical role in the development of cancer and response to cancer therapy. To analyze the mechanism of cancer development and to improve cancer therapy, it is important to assess which genes are downstream components of p53 in cancers, and whether the expression levels of these genes affect p53-mediated %%%apoptosis%%%. In this study, we transduced the wild type p53 gene along with the %%%Apaf%%%-1 and caspase-9 genes via adenovirus vectors into U251 and U373MG glioma cells harbouring a %%%mutated%%% p53, and evaluated the degree of %%%apoptosis%%%. Co-induction of %%%Apaf%%%-1 and caspase-9 genes highly enhanced p53-mediated %%%apoptosis%%% in glioma cells. Induction of wild type p53 enhanced the expression levels of Bax, p21/WAF1, and Fas protein. To determine which gene is activated

by wild type p53 induction and, in turn, activates %%%Apaf%%%-1 and caspase-9, we transduced the Bax, p21/WAF1 or Fas gene via adenovirus vector to U251 cells to achieve a similar expression level as that induced by the Adv for p53 in U251 cells. U251 cells transduced with Fas concomitant with the %%%Apaf%%%-1 and caspase-9 genes underwent drastic %%%apoptosis%%%. This suggests that induction of wild type p53 upregulates Fas, which in turn may play a role in the activation of %%%Apaf%%%-1 and caspase-9. These results are important for analyzing the mechanism of tumour development and for predicting the therapeutic effect of p53 replacement gene therapy in a particular patient.

2/7/21
DIALOG(R)File 5:Biosis Previews(R)


0013546713 BIOSIS NO.: 200200140224
Cancer as an epigenetic disease: DNA methylation and chromatin alterations in human tumours
AUTHOR: Esteller Manel (Reprint); Herman James G
AUTHOR ADDRESS: Cancer Epigenetics Laboratory, Molecular Pathology Program, Centro Nacional de Investigaciones Oncologicas, Melchor Fernandez Almagro 3, 3rd Floor, 28029, Madrid, Spain**Spain
JOURNAL: Journal of Pathology 196 (1): p1-7 January, 2002 2002
MEDIUM: print
ISSN: 0022-3417
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cancer is an epigenetic disease at the same level that it can be considered a genetic disease. In fact, epigenetic changes, particularly DNA methylation, are susceptible to change and are excellent candidates to explain how certain environmental factors may increase the risk of cancer. The delicate organization of methylation and chromatin states that regulates the normal cellular homeostasis of gene expression patterns becomes unrecognizable in the cancer cell. The genome of the transformed cell undergoes simultaneously a global genomic hypomethylation and a dense hypermethylation of the CpG islands associated with gene regulatory regions. These dramatic changes may lead to chromosomal instability, activation of endogenous parasitic sequences, loss of imprinting, illegitimate expression, aneuploidy, and %%%mutations%%%, and may contribute to the transcriptional silencing of tumour suppressor genes. The hypermethylation-associated inactivation affects virtually all of the pathways in the cellular network, such as DNA repair (hMLH1, BRCA1, MGMT, ...), the cell cycle (p16INK4a, p14ARF,

p15INK4b, ...), and %%%apoptosis%%% (DAPK, %%%APAF%%%-1, ...). The aberrant CpG island methylation can also be used as a biomarker of malignant cells and as a predictor of their behaviour, and may constitute a good target for future therapies.

2/7/22
DIALOG(R)File 5:Biosis Previews(R)


0013309271 BIOSIS NO.: 200100481110
Defective cytochrome c-dependent caspase activation in ovarian cancer cell lines due to diminished or absent apoptotic protease activating factor-1 activity
AUTHOR: Wolf Beni B (Reprint); Schuler Martin; Li Wei; Eggers-Sedlet Beth; Lee Wilson; Tailor Pankaj; Fitzgerald Patrick; Mills Gordon B; Green Douglas R
AUTHOR ADDRESS: La Jolla Institute for Allergy and Immunology, 10355 Science Center Dr., San Diego, CA, 92121, USA**USA
JOURNAL: Journal of Biological Chemistry 276 (36): p34244-34251 September 7, 2001 2001
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Apoptosis%%% via the mitochondrial pathway requires release of cytochrome c into the cytosol to initiate formation of an oligomeric apoptotic protease-activating factor-1 (%%%APAF%%%-1) apoptosome. The apoptosome recruits and activates caspase-9, which in turn activates caspase-3 and -7, which then kill the cell by proteolysis. Because inactivation of this pathway may promote oncogenesis, we examined 10 ovarian cancer cell lines for resistance to cytochrome c-dependent caspase activation using a cell-free system. Strikingly, we found that cytosolic extracts from all cell lines had diminished cytochrome c-dependent caspase activation compared with normal ovarian epithelium extracts. The resistant cell lines expressed %%%APAF%%%-1 and caspase-9, -3, and -7; however, each demonstrated diminished %%%APAF%%%-1 activity relative to the normal ovarian epithelium cell lines. A competitive %%%APAF%%%-1 inhibitor may account for the diminished %%%APAF%%%-1 activity because we did not detect dominant %%%APAF%%%-1 inhibitors, altered %%%APAF%%%-1 isoform expression, or %%%APAF%%%-1 deletion, degradation, or %%%mutation%%%. Lack of %%%APAF%%%-1 activity correlated in some but not all cell lines with resistance to %%%apoptosis%%%. These data suggest that regulation of %%%APAF%%%-1 activity may be important

for %%%apoptosis%%% regulation in some ovarian cancers.

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DIALOG(R)File 5:Biosis Previews(R)


0013262678 BIOSIS NO.: 200100434517
%%%Apaf%%%-1 deficiency and neural tube closure defects are found in fog mice
AUTHOR: Honarpour Narimon; Gilbert Sandra L; Lahn Bruce T; Wang Xiaodong; Herz Joachim (Reprint)
AUTHOR ADDRESS: Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX, 75390-9046, USA**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 98 (17): p9683-9687 August 14, 2001 2001
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The forebrain overgrowth %%%mutation%%% (fog) was originally described as a spontaneous autosomal recessive %%%mutation%%% mapping to mouse chromosome 10 that produces forebrain defects, facial defects, and spina bifida. Although the fog mutant has been characterized and available to investigators for several years, the underlying %%%mutation%%% causing the pathology has not been known. Because of its phenotypic resemblance to apoptotic protease activating factor-1 ( %%%Apaf%%%-1) knockout mice, we have investigated the possibility that the fog %%%mutation%%% is in the %%%Apaf%%%-1 gene. Allelic complementation, Western blot analysis, and caspase activation assays indicate that fog mutant mice lack %%%Apaf%%%-1 activity. Northern blot and reverse transcription-PCR analysis show that %%%Apaf%%%-1 mRNA is aberrantly processed, resulting in greatly reduced expression levels of normal %%%Apaf%%%-1 mRNA. These findings are strongly suggestive of the fog %%%mutation%%% being a hypomorphic %%%Apaf%%%-1 defect and implicate neural progenitor cell death in the pathogenesis of spina bifida-a common human congenital malformation. Because a complete deficiency in %%%Apaf%%%-1 usually results in perinatal lethality and fog/fog mice more readily survive into adulthood, these mutants serve as a valuable model with which apoptotic cell death can be studied in vivo.

2/7/24
DIALOG(R)File 5:Biosis Previews(R)

0013129442 BIOSIS NO.: 200100301281

A %%%mutational%%% epitope for cytochrome c binding to the %%%apoptosis%%% protease activation factor-1

AUTHOR: Yu Tianning; Wang Xiaodong; Purring-Koch Cherie; Wei Yen; McLendon George L (Reprint)

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JOURNAL: Journal of Biological Chemistry 276 (16): p13034-13038 April 20, 2001 2001

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Cytochrome c (Cc) binding to %%%apoptosis%%% protease activation factor-1 (%%%Apaf%%%-1) is a critical activation step in the execution phase of %%%apoptosis%%%. Here we report studies that help define the Cc: %%%Apaf%%%-1 binding surface. It is shown that a large number of Cc residues, including residues 7, 25, 39, 62-65, and 72, are involved in the Cc:%%%Apaf%%%-1 interaction. %%%Mutation%%% of residue 72 eliminated Cc activity whereas %%%mutations%%% of residues 7, 25, 39, and 62-65 showed reduced activity in an additive fashion. The implications of this binding model for both recognition and modulation of protein-protein interactions are briefly discussed.

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DIALOG(R)File 5:Biosis Previews(R)



0013038154 BIOSIS NO.: 200100209993

The dependence receptor DCC (deleted in colorectal cancer) defines an alternative mechanism for caspase activation

AUTHOR: Forcet Christelle; Ye Xin; Granger Laure; Corset Veronique; Shin Hwain; Bredesen Dale E; Mehlen Patrick (Reprint)

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JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 98 (6): p3416-3421 March 13, 2001 2001

MEDIUM: print

ISSN: 0027-8424

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The expression of DCC (deleted in colorectal cancer) is often markedly reduced in colorectal and other cancers. However, the rarity of point %%%mutations%%% identified in DCC coding sequences and the lack of a tumor predisposition phenotype in DCC hemizygous mice have raised questions about its role as a tumor suppressor. DCC also mediates axon guidance and functions as a dependence receptor; such receptors create cellular states of dependence on their respective ligands by inducing %%%apoptosis%%% when unoccupied by ligand. We now show that DCC drives cell death independently of both the mitochondria-dependent pathway and the death receptor/caspase-8 pathway. Moreover, we demonstrate that DCC interacts with both caspase-3 and caspase-9 and drives the activation of caspase-3 through caspase-9 without a requirement for cytochrome c or %%%Apaf%%%-1. Hence, DCC defines an additional pathway for the apoptosome-independent caspase activation.

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DIALOG(R)File 5:Biosis Previews(R)


0012979513 BIOSIS NO.: 200100151352
A conserved XIAP-interaction motif in caspase-9 and Smac/DIABLO regulates caspase activity and %%%apoptosis%%%
AUTHOR: Srinivasula Srinivasa M; Hegde Ramesh; Saleh Ayman; Datta Pinaki; Shiozaki Eric; Chai Jijie; Lee Ryung-Ah; Robbins Paul D; Fernandes-Alnemri Teresa; Shi Yigong; Alnemri Emad S (Reprint)
AUTHOR ADDRESS: Center for Apoptosis Research and Department of Microbiology and Immunology, Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, PA, 19107, USA**USA
JOURNAL: Nature (London) 410 (6824): p112-116 1 March, 2001 2001
MEDIUM: print
ISSN: 0028-0836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: X-linked inhibitor-of-%%%apoptosis%%% protein (XIAP) interacts with caspase-9 and inhibits its activity, whereas Smac (also known as DIABLO) relieves this inhibition through interaction with XIAP. Here we show that XIAP associates with the active caspase-9-%%%Apaf%%%-1 holoenzyme complex through binding to the amino terminus of the linker peptide on the small subunit of caspase-9, which becomes exposed after

-1-negative melanomas are invariably chemoresistant and are unable to execute a typical apoptotic programme in response to p53 activation. Restoring physiological levels of %%%Apaf%%%-1 through gene transfer or 5aza2dC treatment markedly enhances chemosensitivity and rescues the apoptotic defects associated with %%%Apaf%%%-1 loss. We conclude that %%%Apaf%%%-1 is inactivated in metastatic melanomas, which leads to defects in the execution of apoptotic cell death. %%%Apaf%%%-1 loss may contribute to the low frequency of p53 %%%mutations%%% observed in this highly chemoresistant tumour type.

2/7/28



0012897379 BIOSIS NO.: 200100069218

Identification of a caspase-2 isoform that behaves as an endogenous inhibitor of the caspase cascade

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JOURNAL: Cancer Research 60 (24): p7039-7047 December 15, 2000 2000
MEDIUM: print
ISSN: 0008-5472
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Procaspase-2 is one of the aspartate-specific cysteine proteases that are activated in response to various apoptotic stimuli. Two isoforms of human procaspase-2 have been described initially. Overexpression of the long isoform (caspase-2L) promotes cell death whereas the short isoform (caspase-2S) antagonizes some apoptotic pathways. In the present study, we identified two additional CASP-2 mRNAs, designated CASP-2L-Pro and CASP-2S-Pro. The proteins encoded by these isoforms corresponded to the prodomain of procaspase-2L, and -2S, in which the last alpha-helix of their caspase recruitment domains was deleted. Caspase-2L-Pro mRNA and protein were detected in a series of human tissues and cell lines. Yeast 2-hybrid assays and immunoprecipitation studies indicated that caspase-2L-Pro can interact with procaspase-2L and the adaptor protein RAIDD/CRADD, but not with FADD/MORT1 or %%%APAF%%%-1 adaptor proteins. The addition of recombinant caspase-2L-Pro negatively interfered with cytochrome c/dATP-mediated activation of the caspase cascade in a cell-free system. In transient expression studies of human B lymphoma

proteolytic processing of procaspase-9 at Asp 315. Supporting this observation, point %%%mutations%%% that abrogate the proteolytic processing but not the catalytic activity of caspase-9, or deletion of the linker peptide, prevented caspase-9 association with XIAP and its concomitant inhibition. We note that the N-terminal four residues of caspase-9 linker peptide share significant homology with the N-terminal tetra-peptide in mature Smac and in the Drosophila proteins Hid/Grim/Reaper, defining a conserved class of IAP-binding motifs. Consistent with this finding, binding of the caspase-9 linker peptide and Smac to the BIR3 domain of XIAP is mutually exclusive, suggesting that Smac potentiates caspase-9 activity by disrupting the interaction of the linker peptide of caspase-9 with BIR3. Our studies reveal a mechanism in which binding to the BIR3 domain by two conserved peptides, one from Smac and the other one from caspase-9, has opposing effects on caspase activity and %%%apoptosis%%%.

2/7/27



0012910368 BIOSIS NO.: 200100082207

Inactivation of the %%%apoptosis%%% effector %%%Apaf%%%-1 in malignant melanoma

AUTHOR: Soengas Maria S; Capodieci Paola; Polsky David; Mora Jaume; Esteller Manel; Opitz-Araya Ximena; McCombie Richard; Herman James G; Gerald William L; Lazebnik Yuri A; Cordon-Cardo Carlos; Lowe Scott W (Reprint)
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JOURNAL: Nature (London) 409 (6817): p207-211 11 January, 2001 2001
MEDIUM: print
ISSN: 0028-0836
DOCUMENT TYPE: Letter
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Metastatic melanoma is a deadly cancer that fails to respond to conventional chemotherapy and is poorly understood at the molecular level. p53 %%%mutations%%% often occur in aggressive and chemoresistant cancers but are rarely observed in melanoma. Here we show that metastatic melanomas often lose %%%Apaf%%%-1, a cell-death effector that acts with cytochrome c and caspase-9 to mediate p53-dependent %%%apoptosis%%%. Loss of %%%Apaf%%%-1 expression is accompanied by allelic loss in metastatic melanomas, but can be recovered in melanoma cell lines by treatment with the methylation inhibitor 5-aza-2'-deoxycytidine (5aza2dC). %%%Apaf%%%

Namalwa cells, overexpression of caspase-2L-Pro weakly induced %%%apoptosis%%%, which was prevented by a D83A/E87A double %%%mutation%%% . In stable selected CASP-2L-Pro-transfected Namalwa cells, overexpression of caspase-2L-Pro delayed apoptotic DNA fragmentation induced by death receptor agonists (anti-Fas antibodies, tumor necrosis factor-alpha) and DNA topoisomerase I- (camptothecin) and II- (etoposide) inhibitors, and prevented etoposide-induced activation of the caspase cascade. These inhibitory effects were not observed in stable transfected cells expressing the D83A/E87A double mutant. Altogether, these data indicated that the caspase-2L-Pro isoform functions as an endogenous %%%apoptosis%%% inhibitory protein that antagonizes caspase activation and cell death.

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DIALOG(R)File 5:Biosis Previews(R)


0012813533 BIOSIS NO.: 200000531846
Disruption of the CED-9cntdotCED-4 complex by EGL-1 is a critical step for programmed cell death in Caenorhabditis elegans
AUTHOR: del Peso Luis; Gonzalez Victor M; Inohara Naohiro; Ellis Ronald E; Nunez Gabriel (Reprint)
AUTHOR ADDRESS: Department of Pathology and Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI, 48109: Gabriel.Nunez@umich.edu, USA**USA
JOURNAL: Journal of Biological Chemistry 275 (35): p27205-27211 September 1, 2000 2000
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In the nematode Caenorhabditis elegans, the apoptotic machinery is composed of four basic elements: the caspase CED-3, the %%%Apaf%%%-1 homologue CED-4, and the Bcl-2 family members CED-9 and EGL-1. The ced-9(n1950) gain-of-function %%%mutation%%% prevents most, if not all, somatic cell deaths in C. elegans. It encodes a CED-9 protein with a glycine-to-glutamate substitution at position 169, which is located within the highly conserved Bcl-2 homology 1 domain. We performed biochemical analyses with the CED-9G169E protein to gain insight into the mechanism of programmed cell death. We find that CED-9G169E retains the ability to bind both EGL-1 and CED-4, although its affinity for EGL-1 is reduced. In contrast to the behavior of wild-type CED-9, the interaction between CED-9G169E and CED-4 is not disrupted by expression of EGL-1.

Furthermore, CED-4 and CED-9G169E co-localizes with EGL-1 to the mitochondria in mammalian cells, and expression of EGL-1 does not induce translocation of CED-4 to the cytosol. Finally, the ability of EGL-1 to promote %%%apoptosis%%% is impaired by the replacement of wild-type CED-9 with CED-9G169E, and this effect is correlated with the inability of EGL-1 to induce the displacement of CED-4 from the CED-9cntdotCED-4 complex. These studies suggest that the release of CED-4 from the CED-9cntdotCED-4 complex is a necessary step for induction of programmed cell death in C. elegans.

2/7/30



0012610036 BIOSIS NO.: 200000328349

Transduction of %%%Apaf%%%-1 or caspase-9 induces %%%apoptosis%%% in A-172 cells that are resistant to p53-mediated %%%apoptosis%%%

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JOURNAL: Biochemical and Biophysical Research Communications 272 (3): p 667-673 June 16, 2000 2000
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: p53 replacement gene therapy has been carried out clinically for cancers with p53 %%%mutations%%%; however, some cancers are resistant to p53 gene therapy. In this study, we transduced A-172 and U251 cells harboring p53 %%%mutations%%% with wild-type p53 using adenovirus vectors to induce wild-type p53 protein at similar expression levels. A-172 cells did not undergo %%%apoptosis%%% after p53 transduction, whereas U251 cells were markedly sensitive to p53-mediated %%%apoptosis%%%. A-172 cells showed higher endogenous expression of Bcl-XL than U251, and transduction of Bcl-XL repressed p53-mediated %%%apoptosis%%% in U251 cells, suggesting that high endogenous expression of Bcl-XL renders A-172 cells, at least in part, resistant to p53-mediated %%%apoptosis%%%. We transduced A-172 cells and U251 cells with the %%%Apaf%%%-1 or caspase-9 genes; both are downstream components of p53-mediated %%%apoptosis%%%. We found that A-172 cells were highly sensitive to %%%Apaf%%%-1- and caspase-9-mediated %%%apoptosis%%%. The results indicate that A-172 cells harboring mutant p53 were not susceptible to p53-mediated %%%apoptosis%%%

, possibly due to high endogenous expression of Bcl-XL. Transduction of %%%Apaf%%%-1 or caspase-9 would override the resistance mechanism of %%%apoptosis%%% in A-172 cells. These findings provide potentially a novel approach in killing cancers that are resistant to p53 replacement gene therapy.

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DIALOG(R)File 5:Biosis Previews(R)


0012435970 BIOSIS NO.: 200000154283
Translocation of C. elegans CED-4 to nuclear membranes during programmed cell death
AUTHOR: Chen Fangli (Reprint); Hersh Bradley M; Conradt Barbara; Zhou Zheng ; Riemer Dieter; Gruenbaum Yosef; Horvitz H Robert
AUTHOR ADDRESS: Department of Biology, WI-525, Whitehead Institute, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA**USA
JOURNAL: Science (Washington D C) 287 (5457): p1485-1489 Feb. 25, 2000 2000
MEDIUM: print
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The Caenorhabditis elegans Bcl-2-like protein CED-9 prevents programmed cell death by antagonizing the %%%Apaf%%%-1-like cell-death activator CED-4. Endogenous CED-9 and CED-4 proteins localized to mitochondria in wild-type embryos, in which most cells survive. By contrast, in embryos in which cells had been induced to die, CED-4 assumed a perinuclear localization. CED-4 translocation induced by the cell-death activator EGL-1 was blocked by a gain-of-function %%%mutation%%% in ced-9 but was not dependent on ced-3 function, suggesting that CED-4 translocation precedes caspase activation and the execution phase of programmed cell death. Thus, a change in the subcellular localization of CED-4 may drive programmed cell death.

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DIALOG(R)File 5:Biosis Previews(R)


0012223612 BIOSIS NO.: 199900483272
Endogenous %%%apoptosis%%% inhibiting proteins
AUTHOR: Rozynkowa Danuta (Reprint); Filip Agata (Reprint)

AUTHOR ADDRESS: Zaklad Genetyki Medycznej AM, Lublin, Poland**Poland
JOURNAL: Postepy Biologii Komorki 26 (3): p561-578 1999 1999
MEDIUM: print
ISSN: 0324-833X
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: Polish

ABSTRACT: Faulty regulations of %%%apoptosis%%% can result in inapropriate suppresion of cell death as occurs f.ex. in some neurodegenerative diseases, cancer and autoimmune conditions. In this article recent discoveries regarding a novel multigene family of inhibitory %%%apoptosis%%% proteins (IAP's) is presented which show homology to baculoviral Iap's. Reported papers will significantly increase our understanding of disease etiology or pathogenesis. Mechanisms inhibiting cellular suicide are highly dependent on BCL-2 family proteins and IAP proteins which significantly increase the number of known %%%apoptosis%%% suppressors. Both are probably involved in the initiation and/or execution of %%%apoptosis%%% and function unter different but overlapping circumstances. It was shown by linkage analysis that deletion/ %%%mutation%%% of 2 different genes named NAIP and SMN, mapped to chromosome 5q13, is responsive for spinal muscular atrophy (SMA), characterized by degeneration of motor neurons leading to muscular atrophy with progressive paralysis. NIAP deletion is responsive for not regulated %%%apoptosis%%% by unknown mechanism whereas loss of SMN dysregulates mRNA biogenesis and is responsive for snRNP metabolism in nerve cells. Cellular members (c-IAP) of human %%%apoptosis%%% inhibitory protein family, orginally identified in baculoviruses, have been presented in relation to gene localizations and tissue expression. The mechanisms of their interaction are connected on associations with TRAF signalling complex in the %%%apoptosis%%% signalling phase and on complexing/blocking specific cysteine containing proteases (caspases) in the executive phase, the structural motiv BIR being indispensable for their interaction. %%%Mutation%%% of caspase-9 through gene targetting in mice results in perinatal letality with markedly enlarged and malformed cerebrum caused by reduced %%%apoptosis%%% and enhanced proliferation during brain development. Casp-9 deficient thymocytes and splenocytes, resistant to several apoptotic stimuli, were surprisinglysensitive to %%%apoptosis%%% induced by UV-irradiation or anti-CD95. Authors compare the requirement for Casp-9 and Casp-3 in different apoptotic settings. SURVIVIN is a new IAP %%%apoptosis%%% inhibitor expressed during development and reexpressed in human cancer. Present investigations are referred in relation to induction of %%%apoptosis%%% by SURVIVIN gene targetting as the coding strand of SURVIVIN gene is exstensively complementary to that of EPR-1. This new target for disrupting cell viability pathways in cancer is being investigated. Recent data of BCL-2

pro- and antiapoptotic family members are shortly reviewed. The structural and functional interactions of BCL-2 proteins with %%%apoptosis%%% protease activating factor (%%%Apaf%%%-1), cytochrome c and caspase regulatory cascade are referred. Succesfull antisens cDNA BCL-2 therapies in progressive lymphoma were shortly presented. Finally author's (A. Filip) last experiments on dysregulated (suppressed) %%%apoptosis%%% in B-CLL lymphocytes accompagnied with stablehigh co-expression of BCL-2 and MYC proteins are presented. Some of reported findings are important in diagnosis (SMN, NIAP in spinal muscular atrophy) and prognosis (SURVIVIN in neoplasia). Further characterization of genes and other regulatory proteins will provide important clues to the understanding of molecular processes controlling cellular suicide and of diseases resulting from dysregulated %%%apoptosis%%%.

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DIALOG(R)File 5:Biosis Previews(R)


0012195709 BIOSIS NO.: 199900455369
Interdigital cell death can occur through a necrotic and caspase-independent pathway
AUTHOR: Chautan Magali; Chazal Genevieve; Cecconi Francesco; Gruss Peter; Golstein Pierre (Reprint)
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JOURNAL: Current Biology 9 (17): p967-970 Sept. 9, 1999 1999
MEDIUM: print
ISSN: 0960-9822
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Programmed cell death in animals is usually associated with apoptotic morphology and requires caspase activation. Necrosis and caspase-independent cell death have been reported, but mostly in experimental conditions that lead some to question their existence in vivo. Loss of interdigital cells in the mouse embryo, a paradigm of cell death during development (1), is known to include an apoptotic (2) and caspase-dependent (3,4) mechanism. Here, we report that, when caspase activity was inhibited using drugs or when %%%apoptosis%%% was prevented genetically (using Hammertoe mutant mice, or mice homozygous for a %%%mutation%%% in the gene encoding %%%APAF%%%-1, a caspase-activating adaptor protein), interdigital cell death still occurred. This cell death was negative for the terminal-deoxynucleotidyl-mediated dUTP nick end-labelling (TUNEL) assay and there was no overall cell condensation.

At the electron microscopy level, peculiar 'mottled' chromatin alterations and marked mitochondrial and membranelesions, suggestive of classical necrotic cell death, were observed with no detectable phagocytosis and no local inflammatory response. Thus, in this developmental context, although caspase activity confers cell death with an apoptotic morphotype, in the absence of caspase activity an underlying mechanism independent of known caspases can also confer cell death, but with a necrotic morphotype. This cell death can go undetected when using %%%apoptosis%%%-specific methodology, and cannot be blocked by agents that act on caspases.

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DIALOG(R)File 5:Biosis Previews(R)


0012155823 BIOSIS NO.: 199900415483
Role of cytochrome c and dATP/ATP hydrolysis in %%%Apaf%%%-1-mediated caspase-9 activation and %%%apoptosis%%%
AUTHOR: Hu Yuanming; Benedict Mary A; Ding Liyun; Nunez Gabriel (Reprint)
AUTHOR ADDRESS: Department of Pathology and Comprehensive Cancer Center, University of Michigan Medical School, 1500 East Medical Center Drive, 4219 CCGC, Ann Arbor, MI, 48109, USA**USA
JOURNAL: EMBO (European Molecular Biology Organization) Journal 18 (13): p 3586-3595 July 1, 1999 1999
MEDIUM: print
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Apaf%%%-1 plays a critical role in %%%apoptosis%%% by binding to and activating procaspase-9. We have identified a novel %%%Apaf%%%-1 cDNA encoding a protein of 1248 amino acids containing an insertion of 11 residues between the CARD and ATPase domains, and another 43 amino acid insertion creating an additional WD-40 repeat. The product of this %%%Apaf%%%-1 cDNA activated procaspase-9 in a cytochrome c and dATP/ATP-dependent manner. We used this %%%Apaf%%%-1 to show that %%%Apaf%%%-1 requires dATP/ATP hydrolysis to interact with cytochrome c, self-associate and bind to procaspase-9. A P-loop mutant (%%%Apaf%%% -1K160R) was unable to associate with %%%Apaf%%%-1 or bind to procaspase-9. %%%Mutation%%% of Met368 to Leu enabled %%%Apaf%%%-1 to self-associate and bind procaspase-9 independent of cytochrome c, though still requiring dATP/ATP for these activities. The %%%Apaf%%%-1M368L mutant exhibited greater ability to induce %%%apoptosis%%% compared with the wild-type %%%Apaf%%%-1. We also show that procaspase-9 can recruit

procaspase-3 to the %%%Apaf%%%-1-procaspase-9 complex. %%%Apaf%%%-1(1-570), a mutant lacking the WD-40 repeats, associated with and activated procaspase-9, but failed to recruit procaspase-3 and induce %%%apoptosis%%%. These results suggest that the WD-40 repeats may be involved in procaspase-9-mediated procaspase-3 recruitment. These studies elucidate biochemical steps required for %%%Apaf%%%-1 to activate procaspase-9 and induce %%%apoptosis%%%.

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DIALOG(R)File 5:Biosis Previews(R)


0012064483 BIOSIS NO.: 199900324143
Structural basis procaspase-9 recruitment by the apoptotic protease-activating factor 1
AUTHOR: Qin Hongxu; Srinivasula Srinivasa M; Wu Geng; Fernandes-Alnemri Teresa; Alnemri Emad S; Shi Yigong (Reprint)
AUTHOR ADDRESS: Princeton, NJ, USA**USA
JOURNAL: Nature (London) 399 (6736): p549-557 June 10, 1999 1999
MEDIUM: print
ISSN: 0028-0836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Caspase-9-mediated %%%apoptosis%%% (programmed cell death) plays a central role in the development and homeostasis of all multicellular organisms. Mature caspase-9 is derived from its procaspase precursor as a result of recruitment by the activating factor %%%Apaf%%%-1. The crystal structures of the caspase-recruitment domain of %%%Apaf%%%-1 by itself and in complex with the prodomain of procaspase-9 have been determined at 1.6 and 2.5 ANG resolution, respectively. These structures and other evidence reveal that each molecule of %%%Apaf%%%-1 interacts with a molecule of procaspase-9 through two highly charged and complementary surfaces formed by non-conserved residues; these surfaces determine recognition specificity through networks of intermolecular hydrogen bonds and van der Waals interactions. %%%Mutation%%% of the important interface residues in procaspase-9 or %%%Apaf%%%-1 prevents or reduces activation of procaspase-9 in a cell-free system. Wild-type, but not mutant, prodomains of caspase-9 completely inhibit catalytic processing of procaspase-9. Furthermore, analysis of homologues from Caenorhabditis elegans indicates that recruitment of CED-3 by CED-4 is probably mediated by the same set of conserved structural motifs, with a corresponding change in the specificity-determining residues.

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DIALOG(R)File 5:Biosis Previews(R)


0011996234 BIOSIS NO.: 199900255894
CIPER, a novel NF kappaB-activating protein containing a caspase recruitment domain with homology to herpesvirus-2 protein E10
AUTHOR: Koseki Takeyoshi; Inohara Naohiro; Chen Shu; Carrio Roberto; Merino Jesus; Hottiger Michael O; Nabel Gary J; Nunez Gabriel (Reprint)
AUTHOR ADDRESS: Dept. of Pathology, University of Michigan Medical School, Ann Arbor, MI, 48109, USA**USA
JOURNAL: Journal of Biological Chemistry 274 (15): p9955-9961 April 9, 1999 1999
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have identified and characterized CIPER, a novel protein containing a caspase recruitment domain (CARD) in its N terminus and a C-terminal region rich in serine and threonine residues. The CARD of CIPER showed striking similarity to E10, a product of the equine herpesvirus-2. CIPER formed homodimers via its CARD and interacted with viral E10 but not with several %%%apoptosis%%% regulators containing CARDs including ARC, RAIDD, RICK, caspase-2, caspase-9, or %%%Apaf%%%-1. Expression of CIPER induced NF-kappaB activation, which was inhibited by dominant-negative NIK and a nonphosphorylable IkappaB-alpha mutant but not by dominant-negative RIP. %%%Mutational%%% analysis revealed that the N-terminal region of CIPER containing the CARD was sufficient and necessary for NF-kappaB-inducing activity. Point %%%mutations%%% in highly conserved residues in the CARD of CIPER disrupted the ability of CIPER to activate NF-kappaB and to form homodimers, indicating that the CARD is essential for NF-kappaB activation and dimerization. We propose that CIPER acts in a NIK-dependent pathway of NF-kappaB activation.

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DIALOG(R)File 5:Biosis Previews(R)


0011797330 BIOSIS NO.: 199900056990
WD-40 repeat region regulates %%%Apaf%%%-1 self-association and procaspase-9 activation
AUTHOR: Hu Yuanming; Ding Liyun; Spencer David M; Nunez Gabriel (Reprint)

AUTHOR ADDRESS: Comprehensive Cancer Cent., Univ. Michigan Med. Sch., Ann Arbor, MI 48109, USA**USA
JOURNAL: Journal of Biological Chemistry 273 (50): p33489-33494 Dec. 11, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The casp9 protein plays a critical role in %%%apoptosis%%% induced by a variety of death stimuli. A regulator of %%%apoptosis%%%, %%%Apaf%%%-1, binds to and activates pro-casp9 in the presence of cytochrome c and dATP, a requirement that is bypassed by deletion of the WD-40 repeats located in the C-terminal half of %%%Apaf%%%-1. In this report, we used constitutively active %%%Apaf%%%-1 mutant lacking the WD-40 repeat region to study the mechanism and regulation of pro-casp9 activation. %%%Mutational%%% analysis revealed that only a small portion of the CED-4 homologous region (residues 456-559) could be deleted without destroying the ability of %%%Apaf%%%-1-(1-559) to activate pro-casp9. %%%Apaf%%%-1 can self-associate to form oligomers. Disruption of %%%Apaf%%%-1 self-association by deletion (DELTA109-559) or %%%mutation%%% of the P-loop region (K149R) abrogated %%%Apaf%%% -1-mediated pro-casp9 activation. Forced oligomerization of the caspase recruitment domain of %%%Apaf%%%-1 was sufficient for pro-casp9 activation. Dimerization of chimeric Fpk-pro-casp9 protein with the dimerizer drug FK1012 induced pro-casp9 processing and %%%apoptosis%%% in cells. Significantly, the C-terminal region containing WD-40 repeats interacted with its N-terminal CED-4 homologous region, as determined by immunoprecipitation experiments. Importantly, expression of the WD-40 repeat region inhibited %%%Apaf%%%-1 self-association and proteolytic activation of pro-casp9. These studies provide a mechanism by which %%%Apaf%%%-1 promotes autoactivation of pro-casp9 through %%%Apaf%%%-1 self-association, a process that is negatively regulated by the WD-40 repeats.

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0011428155 BIOSIS NO.: 199800222402
Blk, a BH3-containing mouse protein that interacts with Bcl-2 and Bcl-xL, is a potent death agonist
AUTHOR: Hegde Ramesh; Srinivasula Srinivasa M; Ahmad Manzoor; Fernandes-Alnemri Teresa; Alnemri Emad S (Reprint)

AUTHOR ADDRESS: Thomas Jefferson Univ., Kimmel Cancer Inst., Bluemle Life Sci. Build. 904, 233 S. 10th St., Philadelphia, PA 19107, USA**USA
JOURNAL: Journal of Biological Chemistry 273 (14): p7783-7786 April 3, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We identified and cloned a novel murine member of the pro-apoptotic Bcl-2 family. This protein, designated Blk, is structurally and functionally related to human Bik and localized to the mitochondrial membrane. Blk contains a conserved BH3 domain and can interact with the anti-apoptotic proteins Bcl-2 and Bcl-xL. Ectopic expression of Blk in mammalian cells induces %%%apoptosis%%%, which can be inhibited by %%%mutations%%% in the BH3 domain and by overexpression of Bcl-2 or Bcl-xL but not by CrmA. The apoptotic activity of Blk is also inhibited by a dominant negative caspase-9, suggesting that Blk induces %%%apoptosis%%% through activation of the cytochrome c-%%%Apaf%%% -1-caspase-9 pathway.

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3/3/1
DIALOG(R)File 5:Biosis Previews(R)


0014940323 BIOSIS NO.: 200400311080
Identification of a congenic mouse line with obesity and body length phenotypes
AUTHOR: Warden Craig H (Reprint); Stone Steven; Chiu Sally; Diament Adam L; Corva Pablo; %%%Shattuck Donna%%%; Riley Robyn; Hunt Steven C; Easlick Juliet; Fisler Janis S; Medrano Juan F
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JOURNAL: Mammalian Genome 15 (6): p460-471 June 2004 2004
MEDIUM: print
ISSN: 0938-8990 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

3/3/2
DIALOG(R)File 5:Biosis Previews(R)

0014855372 BIOSIS NO.: 200400225427
A mutation in PCSK9 causing autosomal-dominant hypercholesterolemia in a Utah pedigree.
AUTHOR: Timms Kirsten M (Reprint); Wagner Susanne; Samuels Mark E; Forbey Kristian; Goldfine Howard; Jammulapati Srikanth; Skolnick Mark H; Hopkins Paul N; Hunt Steve C; %%%Shattuck Donna M%%%
AUTHOR ADDRESS: Myriad Genetics, 320 Wakara Way, Salt Lake City, UT, 84108, USA**USA
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JOURNAL: Human Genetics 114 (4): p349-353 March 2004 2004
MEDIUM: print
ISSN: 0340-6717
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

3/3/3
DIALOG(R)File 5:Biosis Previews(R)


0014680035 BIOSIS NO.: 200400047565
Predisposition locus for major depression at chromosome 12q22-12q23.2.
AUTHOR: Abkevich Victor (Reprint); Camp Nicola J; Hensel Charles H; Neff Chris D; Russell Deanna L; Hughes Dana C; Plenk Agnes M; Lowry Michael R; Richards R Lynn; Carter Catherine; Frech Georges C; Stone Steven; Rowe Kerry; Chau Chi Ai; Cortado Kathleen; Hunt Angelene; Luce Karanina; O'Neil Gayanne; Poarch Jeff; Potter Jennifer; Poulsen Gregg H; Saxton Heidi; Bernat-Sestak Michelle; Thompson Victor; Gutin Alexander; Skolnick Mark H; %%%Shattuck Donna%%%; Cannon-Albright Lisa
AUTHOR ADDRESS: Myriad Genetics, 320 Wakara Way, Salt Lake City, UT, 84108, USA**USA
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JOURNAL: American Journal of Human Genetics 73 (6): p1271-1281 December 2003 2003
MEDIUM: print
ISSN: 0002-9297
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

3/3/4
DIALOG(R)File 5:Biosis Previews(R)

0013901950 BIOSIS NO.: 200200495461
A major predisposition locus for severe obesity at 4p15-p14
AUTHOR: Stone Steven (Reprint); Abkevich Victor (Reprint); Hunt Steven C; Gutin Alexander (Reprint); Russell Deanna L (Reprint); Neff Chris D (Reprint); Riley Robyn (Reprint); Frech George (Reprint); Hensel Charles H (Reprint); Jammulapati Srikanth (Reprint); Potter Jennifer (Reprint); Sexton David (Reprint); Tran Thanh (Reprint); Gibbs Drew (Reprint); Iliev Diana (Reprint); Gress Richard; Bloomquist Brian; Amatruda John; Rae Peter M M; Adams Ted D; Skolnick Mark H (Reprint); %%%Shattuck Donna%%% (Reprint
AUTHOR ADDRESS: Myriad Genetics, Inc., Salt Lake City, UT, 84108, USA**USA
JOURNAL: International Journal of Obesity 26 (Supplement 1): pS9 August, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: Ninth International Congress on Obesity Sao Paulo, Brazil August 24-29, 2002; 20020824
ISSN: 0307-0565
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

3/3/5
DIALOG(R)File 5:Biosis Previews(R)


0013748597 BIOSIS NO.: 200200342108
A major predisposition locus for severe obesity, at 4p15-p14
AUTHOR: Stone Steven (Reprint); Abkevich Victor; Hunt Steven C; Gutin Alexander; Russell Deanna L; Neff Chris D; Riley Robyn; Frech Georges C; Hensel Charles H; Jammulapati Srikanth; Potter Jennifer; Sexton David; Tran Thanh; Gibbs Drew; Iliev Diana; Gress Richard; Bloomquist Brian; Amatruda John; Rae Peter M M; Adams Ted D; Skolnick Mark H; %%%Shattuck%%% %%% Donna%%%
AUTHOR ADDRESS: Myriad Genetics, Inc., 320 Wakara Way, Salt Lake City, UT, 84108, USA**USA
JOURNAL: American Journal of Human Genetics 70 (6): p1459-1468 June, 2002 2002
MEDIUM: print
ISSN: 0002-9297
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

3/3/6

DIALOG(R)File 5:Biosis Previews(R)



0013664960 BIOSIS NO.: 200200258471

Linkage of body mass index to chromosome 20 in Utah pedigrees

AUTHOR: Hunt Steven C (Reprint); Abkevich Victor; Hensel Charles H; Gutin Alexander; Neff Chris D; Russell Deanna L; Tran Thanh; Hong Xiankang; Jammulapati Srikanth; Riley Robyn; Weaver-Feldhaus Jane; Macalma Tess; Richards Maria M; Gress Richard; Francis Mike; Thomas Alun; Frech Georges C; Adams Ted D; %%%Shattuck Donna%%%; Stone Steven

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JOURNAL: Human Genetics 109 (3): p279-285 September, 2001 2001

MEDIUM: print

ISSN: 0340-6717

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

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$104.85 Estimated cost this search

$104.87 Estimated total session cost 2.773 DialUnits

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